DNA Mismatch Repair Happens Only During A Brief Window of Opportunity

December 20, 2011 |

In eukaryotes – the group of organisms that include humans – a key to survival is the ability of certain proteins to quickly and accurately repair genetic errors that occur when DNA is replicated to make new cells.

In a paper published in the December 23, 2011 issue of the journal *Science*, researchers at the Ludwig Institute for Cancer Research and the University of California, San Diego School of Medicine have solved part of the mystery of how these proteins do their job, a process called DNA mismatch repair (MMR).

"One of the major questions in MMR is how MMR proteins figure out which base in a DNA mispair is the wrong one," said Ludwig Institute assistant investigator Christopher D. Putnam, PhD, an adjunct assistant professor of medicine at UC San Diego. "For example, if guanine (G) is inappropriately in a base-pair with thymine (T), is the G or the T the error? Picking the wrong base results in mutations, not fixes."

Using *Saccharomyces cerevisiae*, or baker's yeast, as their model organism, the researchers, led by Richard D. Kolodner, PhD, Ludwig Institute investigator and UCSD professor of medicine and cellular and molecular medicine, discovered that newly replicated DNA produces a temporary signal for 10 to 15 minutes after replication which helps identify it as new – and thus a potential subject for MMR.

The actual signal was not identified, but Putnam said it might be tell-tale nicks in single-stranded DNA or certain proteins associated with replication. The scientists are working to pinpoint the precise signal.

The findings, combined with earlier, published work that visualized MMR in a living cell for the first time, more fully explains how eukaryotes eliminate DNA replication errors, which can result in defects and the development of cancers.

"How eukaryotes identify the newly synthesized strand of DNA is a mystery that has persisted for at least 30 years," said Putnam. "These findings really change our ideas of how MMR works," said

Putnam.

Co-authors include Hans Hombauer and Anjana Srivatsan of the Ludwig Institute for Cancer Research, UCSD Departments of Medicine and Cellular and Molecular Medicine, Institute of Genomic Medicine and UC San Diego Moores Cancer Center.

Funding for this research came from the National Institutes of Health.

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